REMARKS

Claims 109-113, 115-121, 170-175, and 177-181 are pending. Support for the amendments may be found throughout the specification, e.g., at [0115] of corresponding Pub. No. 20070218059.

Rejections under 35 U.S.C. § 112

On page 2 of the Office Action mailed August 10, 2010, the Examiner rejects claims 112 and 121 under 35 U.S.C. § 112, second paragraph, "as being indefinite." Applicants traverse the rejection, nevertheless, in an effort to hasten allowance, the claims have been amended to address the Examiner's concerns.

More specifically, the Examiner finds "active fragment thereof" indefinite in claim 112. Applicants have amended claim 112 to recite "an antigen-binding portion thereof," in tune with the Examiner's suggested language. The Examiner finds "fragment thereof" indefinite in claim 121, because the recited hybridoma does not produce an antibody fragment. Applicants have deleted the recitation of "or fragment thereof." Hence, these rejections may be withdrawn.

On page 3 of the Action, the Examiner rejects claims 109-111, 113, 115-120, 170-174, and 177-181 under 35 U.S.C. § 112, first paragraph, "as containing subject matter which is not described in such a way as to reasonably convey to one skilled in the art that the inventor(s), at the time the application was filed, had possession of the claimed invention." Applicants traverse the rejection.

The Examiner asserts that applicant is not in possession of "any isolated detector of a cell type which identifies on the cell type a cells marker, wherein the cell marker is capable of binding to a GCTM-5 antibody." Applicants have amended the claims to relate to antigen-binding proteins that compete with GCTM-5 antibody for binding to hepatic stem cells. These claims have adequate written description under relevant patent law in which the Federal Circuit has distinguished over the Examiner's cited *Fiers v. Ravel*.

For example, in *Capon v. Eshhar*, 418 F.3d 1349 (Fed. Cir. 2005), the Court upheld claims to DNA sequences although the sequences were not disclosed in the application. The Court explained that "The 'written description' requirement must be applied in the context of the particular invention and the state of the knowledge," and although "the 'written description' requirement states that the patentee must describe the invention; it does not state that every

invention must be described the same way." The court reconciled *Capon* with *Fiers* by acknowledging that the state of the science had changed in the decade between the cases.

Similarly, in *Union Oil Co. v. Atlantic Richfield Co.*, 208 F.3d 9898 (Fed. Cir. 2000), the Court stated that gasoline compositions claimed in terms of a range of their chemical properties, without providing a list of ingredients, satisfied the written description requirement.

Recently, the Court in *Faulkner v. Inglis*, 79 USPQ2d 1001 (2006), upheld the written description to claims to a poxvirus lacking essential genes for use as a vaccine, even though the specification neither identified nor provided any gene sequences or indicated if any such genes were even known in the art. The Court held (*id.* at 1007), that:

> (1) examples are not necessary to support the adequacy of written description (2) the written description standard may be met (as it is here) even where actual reduction to practice of an invention is absent; and (3) there is no *per se* rule that an adequate written description of an invention that involves a biological macromolecule must contains a recitation of known structure.

Regarding the present claims, the state of science regarding the antigen-binding protein/antigen relationship supports the pending claims to an antigen-binding protein that recognizes the antigen that binds with GCTM-5 antibody or an antigen-binding protein that competes with GCTM-5 antibody for binding to the claimed hepatic stem cells. Applicants respectfully request withdrawal of this § 112 rejection.

Rejections under 35 U.S.C. § 102

On page 5 of the Action, the Examiner rejects claims 109-111 and 115-120 under 35 U.S.C. § 102(b) "as being anticipated by Emerson et al (Blood, 1989, v.74, pages 49-55)." Applicants traverse the rejection. The Examiner asserts that Emerson "teaches a monoclonal antibodies, that can bind to surface membrane proteins expressed on the surface of proliferation liver progenitor cells." This is not a correct reading of Emerson, however, which refers to an antibody that specifically binds erythroid progenitor cells, ***not*** the claimed hepatic or pancreatic stem cells. Emerson's Abstract specifically states that:

> A murine monoclonal antibody (MoAb), Ep 3, was raised against enriched fetal liver progenitor cells, which detected all fetal BFU-E and which reacted with the erythropoietic-responsive GM-CSF/IL-3-independent fraction of adult BFU-E and CFU-E. All adult PB BFU-E were Ep 3^- but became Ep 3^+ after stimulation with GM-CSF or IL-3.

It is well-known in the art that BFU (burst forming units) are the progenitors of the ***erythroid*** lineage (Emerson, page 49, col. 1.), not the hepatic lineage of the claimed invention. Thus, although Emerson started with abortus liver cells, these cells were enriched for BFU cells (to derive BFU-E cells) via panning (page 50, col. 1), and only these BFU-E cells were used to generate the monoclonal antibody (*id.*). All the cells that showed Ep 3^+ binding were erythroid cells. Indeed, Emerson concluded that "Ep 3 identified Epo responsive BFU-E whether derived from fetal liver, [peripheral blood] PB, or [bone marrow] BM." Page 52, col.2.

It is well settled that the burden of establishing a *prima facie* case of anticipation resides with the USPTO. *In re Piasecki*, 745 F.2d 1468 (Fed. Cir. 1984). It is the Examiner's position that the antibody of Emerson may inherently have the characteristics of the claimed antigen-binding protein. Inherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient. *In re Oelrich*, 666 F.2d 578 (CCPA 1981). And, in fact, it is clear that the claimed antigen-binding protein is not directed to a cell of erythroid lineage, but to hepatic stem cells. The hepatic stem cells of the present invention are not derived from PB or BM cells, as were Ep 3^+ cells of Emerson. The specificity of GCTM-5 to hepatic stem cells is recited in the claims themselves, and also discussed thoroughly in the specification. For example, the specification states that:

> [0024] The stem cell marker of the present invention identifies a unique sub-population of stem cells that preferably show characteristics of hepatic or pancreatic stem cells or hepatic or pancreatic progenitor cells. More specifically the marker is an early liver marker, which could prove a useful tool for the isolation of liver and pancreatic progenitors for both diseased adult liver and differentiating human embryonic stem cells. Liver and pancreas are embryonically linked and they can interconvert through transdifferentiation. Hence the marker can be found on hepatic and pancreatic cells and progenitor cells. More preferably the marker can be found on hepatoblasts that can differentiate to a liver, hepatic or pancreatic cell and cells of the biliary epithelium.
>
> [0036] The term "hepatic stem cell" may be used interchangeably with "liver stem cell" and encompasses within its scope a hepatoblast, an embryonic liver foetal cell, liver or hepatic progenitor cells or biliary cells, preferably biliary epithelial cells. Most preferably these cells have the capacity to proliferate in the liver. More preferably, the hepatic stem cell is a hepatoblast. The hepatoblast is a multi-potential cell which has the capacity to differentiate to hepatocytes, biliary cells or pancreatic cells. It is now found that the cells identified by the antibody, preferably GCTM-5 antibody or fragment thereof can identify this cell type which has the propensity to differentiate into liver, hepatic or pancreatic cells and especially cells that are actively proliferating. This is evidenced by strong GCTM-5 antibody recognition of cells found in diseased regenerating tissue. The possible

interconversion between liver and pancreatic cells shows that the antibody is capable of being used to identify potential pancreatic cells as well as liver cells.

In conclusion, a careful comparison of Emerson with the claims and specification reveals that Emerson does not, and indeed cannot, support a *prima facie* case of anticipation. It is clear on its face that Emerson's antibody recognizes BFU-E erythroid lineage cells, whereas the claimed antigen-binding protein recognizes hepatic stem cells that are simply not erythroid lineage cells. Moreover, there is no teaching in Emerson regarding hepatic stem cells, hepatoblasts, hepatic progenitor cells, pancreatic stem cells, pancreatic progenitor cells, biliary cells, biliary epithelial cells, hepatic cancer cells. or pancreatic cancer cells.

Hence, because Emerson fails to each and every element of the claimed invention, either explicitly or inherently, as required by *Eli Lilly & Co. v. Zenith Goldline Pharms., Inc.*, 471 F.3d 1369 (Fed. Cir. 2006), this § 102(b) rejection should be withdrawn.

Rejections under 35 U.S.C. § 103

On page 6 of the Office Action, the Examiner rejects claims 170-174 and 177-180 under 35 U.S.C. § 103(a) "as being unpatentable over Emerson et al (Blood, 1989, v.74, pages 49-55) in view of U.S. Patent No. 4,281,061." Applicants traverse the rejection.

That Emerson does not refer to the claimed hepatic stem cell GCTM-5 epitope and GCTM-5 antigen binding proteins has been established above. The teachings of Emerson related to erythroid lineage stem cells provide no suggestion or motivation for the claimed hepatic stem cell GCTM-5 epitope and GCTM-5 antigen binding proteins, nor any suggestion that this marker could exist or how it would be found according to the methods of Emerson, e.g., the enrichment of erythroid lineage BFU-E cells.

The '061 patent is cited for teaching that reagents or pharmaceutical compositions can be provided as kits as a matter of convenience, optimization, and economy of the user, but this reference does not compensate for the dearth of support in the Emerson reference. There is simply nothing in Emerson and the '061 that combines to provide a reasonable expectation of success of achieving an isolated antigen-binding protein that inhibits the binding to a hepatic stem cell of a GCTM-5 antibody that is produced by a hybridoma having ECACC accession number 03101603. Hence, Applicants respectfully request withdrawal of this § 103 rejection.

CONCLUSION

Applicants note with appreciation the Examiner's comments regarding the allowable subject matter of claims 112, 121, 175 and 1818. In view of the foregoing, Applicants submit that the remaining claims are also in condition for allowance, and such allowance is earnestly solicited.

Except for issue fees payable under 37 C.F.R. § 1.18, the Commissioner is hereby authorized by this paper to charge any additional fees during the entire pendency of this application including fees due under 37 C.F.R. §§ 1.16 and 1.17 that may be required, including any required extension of time fees, or credit any overpayment to Deposit Account No. 141138, Deposit Account Name NIXON PEABODY LLP. This paragraph is intended to be a **CONSTRUCTIVE PETITION FOR EXTENSION OF TIME** in accordance with 37 C.F.R. § 1.136(a)(3).

Respectfully submitted,

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